PILOT STUDY OF CEA RNA-LOADED, FLT3 LIGAND-MOBILIZED PERIPHERAL BLOOD ANTIGEN PRESENTING CELLS (FL-PBMC) FOR PATIENTS WITH METASTATIC MALIGNANCIES EXPRESSING CEA

SCIENTIFIC ABSTRACT

This proposal is based upon the premise that a clinically effective T cell mediated immune response can be elicited by activation of T cells specific for tumor-associated or tumor-specific antigens. Carcinoembryonic antigen (CEA), an oncofetal protein overexpressed in the majority (>90%) of gastrointestinal malignancies and over 50% of lung and breast cancers, is such a tumor associated antigen. Recent attempts to induce CEA-specific cellular immune responses utilizing recombinant vaccinia expressing CEA and CEA mRNA loaded dendritic cells (DC) have been shown to be safe. The efficacy of repeated vaccinations with vaccinia vectors is limited by potent vaccinia-specific immune responses. The use of in vitro generated DC requires seven days of culture and considerable human manipulation. The proposed protocol will utilize a cellular product that is easier to obtain with minimal manipulation, autologous FLT3-ligand (FLT3L)-mobilized peripheral blood mononuclear cells loaded *in vitro* with the mRNA encoding CEA.

Flt3L has been shown to be a potent mobilizer of dendritic cells into the peripheral blood and many organs. Our experience with Flt3L suggests that FLT3L can increase peripheral blood dendritic cells to 8-15% of the circulating mononuclear component. Thus, a peripheral blood apheresis product will contain an increased number of dendritic cells. We have previously demonstrated the ability to load dendritic cells *in vitro* with the mRNA encoding CEA and have shown that these DC are potent inducers of tumor-specific T cells *in vitro* and *in vivo*. (The study of DC loaded with CEA mRNA has previously been reviewed by the RAC and approved.) Using CEA RNA-pulsed, autologous FLT3L mobilized peripheral blood mononuclear cells (FL-PBMC) as an enriched source of DC should simplify the process of DC-based immunizations.

Furthermore, a clinical immunotherapy trial using the defined CEA antigen will allow us to characterize the magnitude and persistence of the immune response to this broadly applicable method of generating tumor antigen-specific immune responses. This particular proposal aims to examine the safety, feasibility and immunologic response of active immunotherapy with CEA RNA-pulsed FL-PBMC in patients with metastatic CEA-expressing carcinoma. We would then propose to extend these phase I studies to determine if human CEA RNA-pulsed FL-PBMC are effective mediators of tumor-specific immunotherapy.

The specific objectives of this proposal are:

2.1. Primary Objective

a. To evaluate the safety and feasibility of administering CEA RNA-loaded Flt3L-mobilized peripheral blood antigen presenting cells (FL-PBMC) to patients with metastatic malignancies expressing CEA.

2.2. Secondary Objectives

a. To evaluate the CEA-specific immune response induced by active immunotherapy with CEA RNA-loaded Flt3L-mobilized peripheral blood antigen presenting cells (FL-PBMC) in these patients.